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(54) NON-CHLOROFLUOROCARBON AEROSOL FORMULATIONS

FLUORCHLORKOHLENWASSERSTOFFREIE AEROSOLFORMULIERUNGEN

FORMULATIONS POUR DES AEROSOLS NE CONTENANT PRATIQUEMENT PAS DE CHLOROFLUOROCARBONES

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Description

INTRODUCTION TO THE INVENTION

The present invention is directed at aerosol formulations which are substantially free of chlorofluorocarbons (CFC's). More specifically, the present invention is directed at formulations substantially free of CFC's and having particular utility in medicinal applications, especially in metered dose pressurized inhalators (MDI's).

Metered dose inhalators have proven to be an effective method for delivering medicaments orally and nasally. They have been used extensively for delivering bronchodilating and steroidal compounds to asthmatics and may also be useful for delivering other compounds such as pentamidine and non-bronchodilator anti-inflammatory drugs. The rapid onset of activity of compounds administered in this manner and the absence of any significant side effects have resulted in a large number of compounds being formulated for administration via this route. Typically, the drug is delivered to the patient by a propellant system generally comprising one or more propellants which have the appropriate vapor pressure and which are suitable for oral or nasal administration. The more preferred propellant systems typically comprise propellant 11, propellant 12, propellant 114 or mixtures thereof. Often the vapor pressure of the propellant systems is adjusted by admixing a liquid excipient with the propellant.

However, propellants 11, 12 and 114 belong to a class of compounds known as chlorofluorocarbons, which have been linked to the depletion of ozone in the atmosphere. It has been postulated that ozone blocks certain harmful UV rays and that a decrease in the atmospheric ozone content will result in an increase in the incidence of skin cancer. In the 1970's certain steps were taken to reduce the CFC emissions from aerosols. Other propellants, such as hydrocarbons, were used, or the product was delivered in a different manner. Because CFC usage in medicinal applications is relatively low i.e. less than 1% of total CFC emissions, and because of the health benefits associated with metered dose inhalators, steps were not taken at that time to restrict the use of CFC propellants in metered dose inhalators.

However, continuing and more sophisticated ozone measurements have indicated that the earlier restrictions in CFC usage were insufficient and that additional, significant steps should be taken to drastically reduce CFC emissions. Recently, recommendations have been made that CFC production be virtually discontinued by the end of this century. As a result, it may not be possible to continue to use CFC propellants in the intermediate and long term. While some efforts have been made to use non-pressurized metered dose inhalators, many of these devices have not been completely successful. Many do not deliver uniform doses, are mechanically complex, do not provide the 100-200 doses per unit of current aerosol containers, are difficult for individuals to utilize, and are bulky and/or cumbersome for the patients to use, particularly when they have an acute need for the medication.

As a result, there is a need for aerosol formulations which are substantially free of CFC's. Non-CFC propellants systems must meet several criteria for pressurized metered dose inhalators. They must be non-toxic, stable and non-reactive with the medicament and the other major components in the valve/actuator. One propellant which has been found to be suitable is CF_3-CH_2F-CF_3, also known as Freon 227, HFA 227, HFC 227 or 1,1,1,2,3,3,3 heptafluoropropane. However, certain physical properties, i.e., polarity and solubility, of HFC 227 differ from those of commonly used CFC propellants. Commonly used surfactants may be insoluble in HFA 227. Moreover, where the medicament is to be delivered as a solution, the medicament may not be readily soluble in this propellant. The polarity difference between HFC 227 and the previously used CFC propellants may result in a different delivery of the medicament when HFC 227 replaces a CFC propellant. The medicament may cream, settle or agglomerate in the non-CFC propellant even though this did not occur in the CFC propellant.

The use of HFA 227 previously has been disclosed for use in medicinal inhalators. European Patent Publication No. 0 384 371 is directed at the combination of propellant 227 and propane, butane, isobutane, Me_2O and/or F_2CHMe.

Research Disclosure No. 30161, May, 1989 discloses that non-CFC propellants, such as fluorohydrocarbons may be used in pressurized medicaments delivered directly to the lungs, e.g. bronchodilators.

Other publications have been directed at the use of other fluorohydrocarbons, such as HFC 134a, for aerosol propellants. European Patent Publication No. 0 372 777 is directed at medicinal aerosol formulations incorporating HFC 134a and an adjuvant having a higher polarity than the propellant. This publication lists several possible adjuvants and surfactants for use in combination with the propellant and the medicament.

International patent application No. WO 91/04011 discloses the combination of HFC 134a and a powdered medicament pre-coated with a non-perfluorinated surfactant prior to dispersing the powdered medicament in the propellant. Pages 6-7 of the publication list suitable surfactants for use with the propellant. A perfluorinated adjuvant optionally could be added. However, the pre-coating of the medicament may not be advantageous, since it adds an additional, complex step to the manufacturing process.

U.S. Patent No. 4,174,295 discloses the combination of HFC 134a with various chlorofluorocarbons and optionally a saturated hydrocarbon. U.S. Patent No. 2,885,427 discloses the use of HFC-134a as an aerosol propellant. U.S. Patent No. 3,261,748 discloses the use of HFC-134a for anesthesia. U.S. Patent Nos. 4,129,603, 4,311,863, 4,851,595 and European Publication No. 379,793 also disclose the use of HFC-134a as an aerosol propellant.

However, the specific combinations noted above may not provide the desired solubility, stability, low toxicity, exact dosage, correct particle size (if suspension) and/or compatibility with commonly used valves assemblies of metered dose inhalers. Further, prior art use of non-CFC propellants such as HFA 227 is in combination with surfactants, excipients and other such aerosol components.

SUMMARY OF THE INVENTION

Accordingly, the present invention is directed at a non-toxic formulation substantially free of CFC's having improved stability and compatibility with the medicament and which is relatively easily manufactured.

The present invention also is directed at formulations which may be utilized in present aerosol filing equipment with only relatively minor modifications and without pre-coating the medicament.

The invention provides an aerosol formulation consisting of:

A. an effective amount of a medicament;
B. 1,1,1,2,3,3,3-heptafluoropropane; and
C. optionally, one or more components selected from one or more of the following:
preservatives;
buffers;
antioxidants;
sweeteners; and
taste masking agents.

The invention is of particular utility where the medicament is albuterol, mometasone furoate or beclomethasone dipropionate, and salts and clathrates thereof.

A useful formulation range comprises:

A. 1,1,1,2,3,3,3-heptafluoropropane	99-99.99 wt%
B. medicament	0.01-1 wt%

The present invention also is directed at the use of an effective amount of an aerosol formulation of the invention comprising a medicament selected from albuterol, mometasone furoate, beclomethasone dipropionate, and salts and clathrates thereof in treating asthma in mammals .

DETAILED DESCRIPTION OF THE INVENTION

The formulations of the present invention all utilize propellant 227 in combination with the medicament.

The medicaments of the present invention may include any pharmaceutically active compounds which are to be delivered by oral inhalation or nasally. Typical classes of compounds include bronchodilators, anti-inflammatory compounds, antihistamines, antiallergics, analgesics, antitussives, anti-anginal medications, steroids, corticosteroids, vasoconstrictors and antibiotics. Specific compounds within these classes of compounds are albuterol, mometasone furoate, beclomethasone dipropionate, isoproterenol, heparin, terbutaline, rimiterol, perbuterol, disodium cromoglycate, isoprenaline, adrenaline, pentamidine and ipratropium bromide. These compounds may be utilized either as the free base, as a salt, or as a clathrate, depending upon the stability and solubility of the active compound in the specific formulation. When clathrates are utilized, P-11 and hexane clathrates are particularly preferred.

Where the active compound forms a suspension, the particle size should be relatively uniform, with substantially all the particles preferably ranging between about 0.1-25 microns, preferably 0.5-10 microns, more preferably 1-5 microns. Particles larger than 25 microns may be held up in the oropharyngeal cavity, while particles smaller than about 0.5 micron preferably are not utilized, since they would be more likely to be exhaled and, therefore, not reach the lungs of the patient.

The formulations of the present invention may be filled into the aerosol containers using conventional filling equipment. Since propellant 227 may not be compatible with all elastomeric compounds currently utilized in present aerosol valve assemblies, it may be necessary to substitute other materials, such as white buna rubber, which mitigate the adverse effects of propellant 227 on the valve components.

To assure uniform dispersion of the active ingredient, the formulations typically will include the following components:

	Range (wt%)	Preferred Range (wt%)	Most Preferred Range (wt%)
Medicament	0.01 - 1	0.03 - 0.7	0.05 - 0.5
Propellant	99 - 99.99	99.3 - 99.97	99.5 - 99.95

Depending on the particular application, the container may be charged with a predetermined quantity of formulation for single or multiple dosing. Typically, the container is sized for multiple-dosing, and, therefore, it is very important that the formulation delivered is substantially uniform for each dosing. For example, where the formulation is for bronchodilation, the container typically is charged with a sufficient quantity of the formulation for 200 charges.

Suitable suspensions may be screened in part by observing several physical properties of the formulation, i.e. the rate of particle agglomeration, the size of the agglomerates and the rate of particulate creaming/settling and comparing these to an acceptable standard. Suitable solutions may be screened by observing the solubility of the medicament over the entire recommended storage temperature range.

Suspensions of the present invention preferably may be prepared by either the pressure filling or cold filling procedures well-known in the art.

For metered dose inhalators, suspensions may be particularly preferred for efficacy and stability considerations.

Those skilled in the art may choose to add one or more preservative, buffer, antioxidant, sweetener and/or flavours or other taste masking agents depending upon the characteristics of the formulation.

Examples I and II below further describe the present invention.

EXAMPLE I

Mometasone Furoate	0.1
HFC-227	99.9

EXAMPLE II

Beclomethasone Dipropionate	0.1
HFC-227	99.9

While the examples above have been directed at albuterol, albuterol sulfate, mometasone furoate, beclomethasone dipropionate and beclomethasone dipropionate clathrates, it is contemplated that other orally or nasally administered medicaments could be utilized. Similarly, it is contemplated that excipients and surfactants other than those exemplified may be utilized.

Claims

1. An aerosol formulation consisting of:

   A. an effective amount of a medicament;
   B. 1,1,1,2,3,3,3-heptafluoropropane; and
   C. optionally, one or more components selected from one or more of the following:
      preservatives;

buffers;
antioxidants;
sweeteners; and
taste masking agents.

2. A formulation according to Claim 1 wherein the medicament is selected from albuterol, mometasone furoate, beclomethasone dipropionate, isoproterenol, heparin, terbutaline, rimiterol, perbuterol, disodium cromoglycate, isoprenaline, adrenaline, pentamidine, ipratropium bromide, and salts and clathrates thereof.

3. A formulation according to Claim 2 wherein the medicament is selected from albuterol, albuterol sulfate, beclomethasone dipropionate, beclomethasone dipropionate clathrates, and mometasone furoate.

4. A formulation according to any preceding claim containing 0.01 to 1 percent by weight medicament.

5. A formulation according to Claim 4 containing 0.03 to 0.7 percent by weight medicament.

6. A formulation according to Claim 5 containing 0.05 to 0.5 percent by weight medicament.

7. A formulation according to any preceding claim wherein the medicament is a powder having a mean particle size of 1-5 microns.

Patentansprüche

1. Aerosol-Formulierung, bestehend aus:

A. einer wirksamen Menge eines Medikamentes;
B. 1,1,1,2,3,3,3-Heptafluorpropan und
C. gegebenenfalls einer oder mehreren Komponenten, ausgewählt aus einer oder mehreren der folgenden:
Konservierungsmittel;
Puffer;
Oxidationsschutzmittel;
Süßstoffe und
geschmacksmaskierenden Mitteln.

2. Formulierung nach Anspruch 1, wobei das Medikament aus Albuterol, Mometasonfuroat, Beclomethasondipropionat, Isoproterenol, Heparin, Terbutalin, Rimiterol, Perbuterol, Dinatriumcromoglycat, Isoprenalin, Adrenalin, Pentamidin, Ipratropiumbromid und deren Salze und Clathraten ausgewählt ist.

3. Formulierung nach Anspruch 2, wobei das Medikament aus Albuterol, Albuterolsulfat, Beclomethasondipropionat, Beclomethasondipropionatclathraten und Mometasonfuorat ausgewählt ist.

4. Formulierung nach einem der vorhergehenden Ansprüche, die 0,01 bis 1 Gew.-% Medikament enthält.

5. Formulierung nach Anspruch 4, die 0,03 bis 0,7 Gew.-% Medikament enthält.

6. Formulierung nach Anspruch 5, die 0,05 bis 0,5 Gew.-% Medikament enthält.

7. Formulierung nach einem der vorhergehenden Ansprüche, wobei das Medikament ein Pulver mit einer mittleren Teilchengröße von 1 bis 5 µm ist.

Revendications

1. Formule en aérosol consistant en

A. une quantité efficace d'un médicament ;
B. du 1,1,1,2,3,3,3-heptafluoropropane ; et
C. facultativement, un ou plusieurs composants sélectionnés parmi un ou plusieurs de ceux qui suivent :
conservateurs ;
tampons ;

anti-oxydants
édulcorants et
agents masquant le goût.

2. Formule selon la revendication 1 où le médicament est sélectionné parmi l'albutérol, le furoate de mométhasone, le dipropionate de béclométhasone, l'isoprotérénol, l'héparine, la terbutaline, le rimitérol, le perbutérol, le cromoglycate disodique, l'isoprénaline, l'adrénaline, la pentamidine, le bromure d'ipratropium et leurs sels et clathrates.

3. Formule selon la revendication 2 où le médicament est sélectionné parmi l'albutérol, le sulfate d'albutérol, le dipropionate de béclométhasone, les clathrates de dipropionate de béclométhasone et le fuorate de mométhasone.

4. Formule selon toute revendication précédente contenant 0,01 à 1% en poids du médicament.

5. Formule selon la revendication 4 contenant 0,03 à 0,7% en poids du médicament.

6. Formule selon la revendication 5 contenant 0,05 à 0,5% en poids du médicament.

7. Formule selon toute revendication précédente où le médicament est une poudre ayant une grandeur moyenne de particule de 1-5 microns.